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Date of application : 24-07-2002
Application No : 555/MAS/2002
Applicants : Dr. Reddy's Laboratories Limited,
An Indian Company having its registered office at
7-1-27, Ameerpet, Hyderabad-500 016,
A.P., India.

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Dated this the 08th day of July 2005
17th day of Asadha, 1927(Saka)

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FORM-2
THE PATENTS ACT, 1970

COMPLETE SPECIFICATION
(SECTION 10)

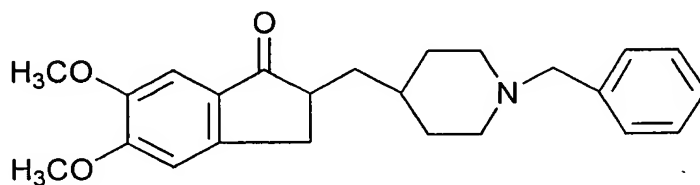
An Improved Process for the Preparation of
2,3-dihydro-5, 6-dimethoxy-2 [[1-(phenyl methyl)-4-
piperidinyl] methyl]-1H-inden-1-one
(Donepezil)

Dr. Reddy's Laboratories Limited,
An Indian Company having its registered office at
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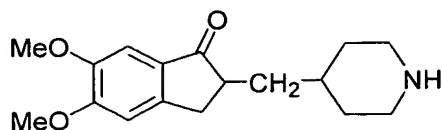
The following specification particularly describes the nature of this invention and the manner on which it is to be performed.

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The present invention relates to an improved and convenient process for the preparation of Donepezil, which is chemically known as 2,3-dihydro-5, 6-dimethoxy-2 [[1-(phenyl methyl)-4-piperidinyl] methyl]-1H-inden-1-one and represented by Formula (I). More specifically the present invention relates to an improved process for the preparation of a key intermediate 5,6-dimethoxy-2-piperidin-4-ylmethyl-indan-1-one, which is represented as Formula (VI) by an economically, and industrially preferable method.



Formula (I)



Formula (VI)

BACK GROUND OF THE INVENTION:

Donepezil hydrochloride is an acetyl cholinesterase (AChE) inhibitor used for treatment of patients with senile dementia of Alzheimer's type (DAT). Alzheimer senile dementia is accompanied by lowering in cholinergic hypofunction caused due to deficiency of acetyl choline enzyme in brain. Donepezil is the first promising agent for the treatment of this type of disease. This new drug was approved first in US in 1997 and later in 64 countries. It acts as an anti acetyl cholin esterase and increases the acetyl choline present

in the brain. It is effective for the treatment of various conditions involving memory loss such as Alzheimer's disease and other neuro degenerative disorders.

US Patent 4,895,481 claims Donepezil, its related compounds along with their pharmaceutical acceptable salts including composition and method of treatment using them. The process for the preparation of Donepezil is disclosed by the aforesaid product patent comprises the conversion of 1-benzyl-4-piperidinone to 1-benzyl-4-piperidine carboxaldehyde in the presence of n- butyl lithium, which on further reaction with 5,6-dimethoxy-1-indanone in the presence of strong base such as lithium diisopropylamide under inert atmosphere followed by reduction of the obtained compound to give the title compound of Formula (I) with an over all yield of 27.4%.

US Patent 5,606,064 also discloses the process for the preparation of Donepezil, which comprises reacting 5,6-dimethoxy indanone and pyridine-4-carboxaldehyde to yield 5,6 dimethoxy-2-pyridin-4-yl methylene-indan-1-one, which upon condensation with benzyl bromide followed by reduction of the obtained compound with platinum oxide to afford the title compound of Formula (I) with an overall yield of 58.5%.

WO 97/22584 also discloses the process for the preparation of Donepezil of Formula (I) in the preparations 1 to 3 and example 1 to 6, with an alleged overall yield of 19.3% starting from Pyridine-4- carboxaldehyde.

The prior art procedures for the preparation of Donepezil are having some disadvantages such as usage of hazardous raw materials like lithium diisopropyl amine and n-butyl lithium. These procedures also involve the usage of very costly raw material, platinum oxide for reduction. The processes involve the chromatographic separations for isolation of intermediates and yielded in very low. The processes for the preparation of Donepezil

are also involving more number of steps, which in turn resulted the less cost effective processes. These are less viable for commercial production as the usage of n-butyl lithium is at very low temperature (i.e., -80°C).

Additionally, the process for the preparation of Donepezil was also disclosed in EP 534859 in example 9A1 and US 6252081B1 in example 1, 2, and 3 with satisfactory yield of 82.5%, but this process also comprises of the steps utilizing hazardous material such as, sodium hydride in two of steps and highly expensive material, such as platinum oxide in the final step.

These foregoing problems, directed us towards the present invention, which is the convenient and economic process for the preparation of the compound of the Formula (I). The present invention more specifically related to provide a novel process for the preparation of a key intermediate, depicted as Formula (VI) in high yield using the palladium catalyzed hydrogenation.

The process of the present invention avoids the usage of hazardous and costly raw materials such as n-butyl lithium and platinum oxide. The present process involves less number of steps and resulted the key intermediate of Formula (VI) in 100% yield. Thus, the present process is more cost effective, non-hazardous and easily scalable over the prior art processes.

SUMMARY OF THE INVENTION:

The present invention relates to an improved and convenient process for the preparation of 2,3-dihydro-5, 6-dimethoxy-2 [[1-(phenyl methyl)-4-piperidinyl] methyl]-1H-inden-1-one (Donepezil) and represented by Formula (I).

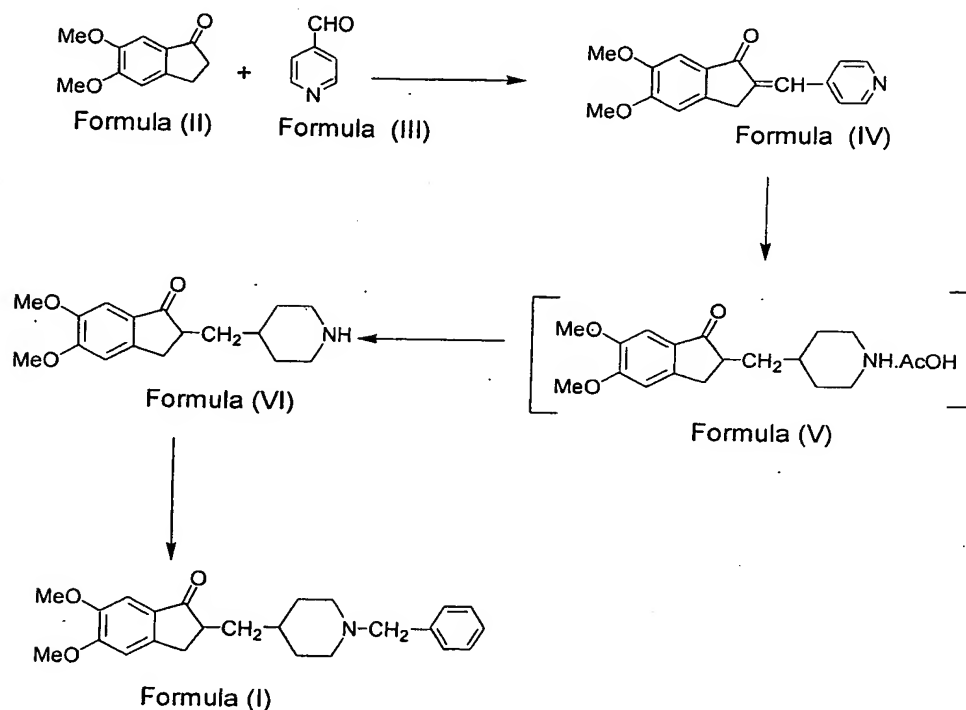
More particularly the improved process of the present invention comprises the preparation of key intermediate of Formula (VI) by palladium-catalyzed hydrogenation of compound of Formula (IV), followed by its conversion to Donepezil with an overall yield of 83.03%.

The process of the present invention avoids the usage of hazardous and expensive raw materials such as n-Butyl lithium, phosphorous pentaoxide and lithium diisopropylamine. The present process is more cost effective, non-hazardous and easily scalable to commercial quantities over prior art references.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to an improved and convenient process for the preparation of 2,3-dihydro-5, 6-dimethoxy-2 [[1-(phenyl methyl)-4-piperidinyl] methyl]-1H-inden-1-one (Donepezil) of Formula (I), which comprises the reaction of 5,6-dimethoxy indanone of Formula (II) with pyridine-4-carboxaldehyde of Formula (III) in the presence of an organic solvent to afford 5,6 dimethoxy-2- (pyridin-4-yl)-methylene indan-1-one of Formula (IV). The compound of Formula (IV) is hydrogenated under palladium carbon catalyst in the presence of acetic acid in methanol to afford the acetate salt of Formula (V), which is in situ converted to the key intermediate 5,6-dimethoxy-2-piperidin-4-yl-methyl indan-1-one of Formula (VI). Further reaction of Formula (VI) with benzyl

bromide in a solvent in the presence of base yields Donepezil of Formula (I) in over all yield of 83%. The relevant synthetic scheme is schematically depicted as follows:



Accordingly, an improved process for the preparation of Donepezil of Formula (I) comprises:

- refluxing the mixture of 5,6-dimethoxy indanone of Formula (II) and pyridine-4-carboxaldehyde of Formula (III) in a solvent such as toluene using p-toluene sulfonic acid as a catalyst till reaction substantially completes;
- cooling the reaction mixture of step (a) to ambient temperature accompanied by filtering the solid;

- c) suspending the solid obtained in step (b) in aqueous basic solutions comprising of sodium hydroxide, sodium carbonate, sodium bicarbonate, potassium hydroxide, potassium carbonate or potassium bicarbonate, preferably aqueous sodium bicarbonate solution followed by stirring for 1-2 hours;
- d) filtering the solid obtained in step (c) to afford 5,6 dimethoxy-2-(pyridin-4-yl)-methylene indan-1-one of Formula (IV);
- e) suspending the compound of Formula (IV) and Palladium on carbon in alcoholic solvent comprising of methanol, ethanol, n-propanol, isopropanol, n-butanol or tertiary butanol, preferably methanol in presence of acetic acid in hydrogenation vessel;
- f) heating the reaction mixture of step (e) under 1-5 atmospheric hydrogen pressure at a temperature of 40 to 90° C, preferably at a temperature of 60-65°C till the reaction substantially completes;
- g) cooling of the reaction mass of step (f) to ambient temperature followed by filtering the catalyst;
- h) distilling the solvent from the filtrate obtained in step (g) to get the residue;
- i) dissolving the residue obtained in step (h) in water and followed by washing with a chloro solvent comprising of dichloromethane, dichloroethane, chloroform or carbon tetrachloride, preferably dichloromethane and separating the aqueous layer;
- j) adjusting the pH of the aqueous layer of step (i) to 9 to 14 with a base solution comprising of sodium hydroxide, sodium carbonate, sodium

bicarbonate, potassium hydroxide, potassium carbonate or potassium bicarbonate, preferably aqueous potassium hydroxide solution;

- k) extracting the compound from the basified aqueous layer of step (j) with an organic solvent comprising of dichloromethane, chloroform, dichloroethane, toluene, ethyl acetate, isopropyl ether, methyl tertiary butyl ether, diethyl ether or petroleum ether, preferably dichloromethane;
- l) distilling the solvent from the reaction solution of step (k) followed by triturating the residue in non-polar organic solvents comprising of n-hexane, n-heptane, cyclohexane, cyclo heptane or petroleum ether, preferably petroleum ether or ether solvents comprising of di ethyl ether, di isopropyl ether, di isobutyl ether or methy tertiary butylether to afford 5,6-dimethoxy-2-piperidin-4-yl methyl-indan-1-one of Formula (VI);
- m) reacting the compound of Formula (VI) with benzyl bromide in alcoholic solvents comprising of methanol, ethanol isopropanol, butanol or ketone solvents comprising of acetone, ethylmethyl ketone, 2-butanone in the presence of a base inorganic base comprising of sodium carbonate, sodium bicarbonate, potassium carbonate or potassium bicarbonate or organic base comprising of triethyl amine, tributyl amine, tertiary butyl amine or pyridine at a temperature of 30-80°C, preferably at 50°C till the reaction substantially completes;
- n) cooling the reaction mass to ambient temperature and followed by filtering the mass;

- o) diluting the filtrate obtained in step (n) with water and further extracting the compound into ether solvents comprising isopropyl ether, methy tertiary butylether or diethyl ether or aromatic hydrocarbon solvents comprising of toluene, benzene, ethyl benzene, xylene, preferably toluene or aliphatic hydrocarbon solvents comprising of hexane, cyclohexane or petroleum ether.
- p) distilling the solvent from the reaction solution of step (o) followed by triturating the residue in non-polar organic solvents comprising of n-hexane, n-heptane, cyclohexane, cyclo heptane or petroleum ether, preferably petroleum ether or ether solvents comprising of di ethyl ether, di isopropyl ether, di isobutyl ether or methy tertiary butylether to afford the title compound Donepezil of Formula (I).

The strength of aqueous base solution mentioned in step © of the above process is varied from 5 to 20%, preferably 10% w/v of aqueous sodium carbonate solution.

The reduction of compound of Formula (IV) mentioned in the step (e) of the above process has done using 5% or 10% Palladium over charcoal to result the acetate salt of Formula (V) in 100% yield, which in situ is converted to the key intermediate of Formula (VI).

The strength of aqueous base solution mentioned in step (j) of the above process is varied from 5 to 20%, preferably 10% w/v of aqueous potassium hydroxide solution.

Hence the present invention provides a cost effective and eco friendly process, which involves the usage of Palladium carbon instead of Platinum oxide for reduction of

compound of Formula (IV), followed by condensation with benzyl bromide to afford Donepezil.

The process of present invention also avoids the usage of hazardous raw materials, such as n-Butyl lithium, phosphorous pentoxide, lithium diisopropylamine (LDA) as mentioned in the prior art.

The Donepezil obtained in the above process of the present invention is having high purity with 92% of overall yield.

The following examples are illustrating the invention but do not limit the effective scope of the claims in any way.

Experimental Section:

Example-1:

Preparation of 5, 6 Dimethoxy-2- (pyridine-4yl)-methylene-indan-1 one (Compound IV):

5, 6 Dimethoxy indanone (100 grams), Pyridine-4-carboxaldehyde (78.0 grams) and p-toluene sulfonic acid (138.4 grams) were suspended in toluene (1250 ml) and heated to reflux using water separator for 6 hours. The resulting mass was cooled to 25-40°C and the solid was filtered off under suction. Further the wet solid was suspended in aqueous 10% sodium carbonate solution (1200 ml) and stirred for 30-60 minutes. The resulting pale yellow precipitate solid was filtered off under suction, washed with water (1000 ml) and dried at a temperature of 80°C to afford 5,6 Dimethoxy-2-(pyridin-4yl)-methylene-indan-1-one (Weight: 140 grams, 95.8%).

Example-2:**Preparation of 5,6-Dimethoxy-2-piperidin-4-yl methyl-indan-1-one****(Compound VI)**

5,6-Dimethoxy-2-(pyridin-4-yl) methylene indan-1-one (IV, 50.0 grams), 5% palladium on activated carbon (12.5 grams), acetic acid (12.8 grams) and Methanol (875 ml) were taken in 2.0 liter hydrogenation flask and applied hydrogen gas in inert atmosphere. The hydrogenation was carried out at hydrogen pressure of 3-4 atmospheres at 60-65°C for 8 hours. Then the flask was cooled to room temperature and the catalyst was filtered off. The solvent was distilled off from the filtrate and resulting residue was dissolved in water (1000 ml). The aqueous solution thus obtained was washed with Dichloromethane. Further, the pH of the aqueous layer was adjusted to ~13.0 and extracted the compound into Dichloromethane. The combined dichloromethane layer was dried over sodium sulfate and concentrated under vacuum to get the residue. Thus resulted residue was triturated petroleum ether to afford 5,6 Dimethoxy-2-piperidinyl-4-yl methyl-indan-1-one (Weight: 49grams, 95.3%).

Example-3:**Preparation of 2,3-dihydro-5, 6-dimethoxy-2[[1-(phenyl methyl)-4-piperidinyl]methyl]-1H-inden-1-one (Donepezil)(I):**

5,6 Dimethoxy-2-piperidinyl-4-yl methyl indan-1-one (VI, 20 grams) was suspended in ethanol (300 ml) and stirred at a temperature of 50°C to get the clear solution. Sodium carbonate (4.40 grams), Benzyl Bromide (11.8 grams) was added slowly drop wise at a temperature of 50°C. Then, the reaction mass was stirred at a temperature of 55-60°C for 6 hours and cooled the mass to room temperature. The reaction mass was filtered off and

water (300 ml) was added to the filtrate. The compound was extracted from the resulting aqueous solution using toluene (250 ml). The toluene layer was concentrated under vacuum to get the residue. The residue was triturated in petroleum ether to afford the title compound.

(Weight: 24.2 grams, 92.3%).

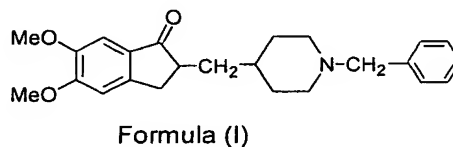
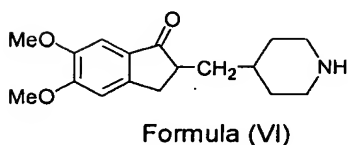
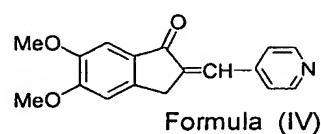
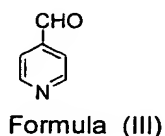
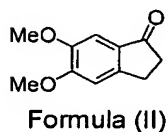
We claim:

1. An improved process for the preparation of 2,3-dihydro-5, 6-dimethoxy-2[[1-(phenyl methyl)-4-piperidinyl]methyl]-1H-inden-1-one (Donepezil) of Formula (I), which comprises:
 - a) refluxing the mixture of 5,6-dimethoxy indanone of Formula (II) and pyridine-4-carboxaldehyde of Formula (III) in a solvent such as toluene using p-toluene sulfonic acid as a catalyst till reaction substantially completes;
 - b) cooling the reaction mixture of step (a) to ambient temperature accompanied by filtering the solid;
 - c) suspending the solid obtained in step (b) in aqueous basic solutions comprising of sodium hydroxide, sodium carbonate, sodium bicarbonate, potassium hydroxide, potassium carbonate or potassium bicarbonate, preferably aqueous sodium bicarbonate solution followed by stirring for 1-2 hours;
 - d) filtering the solid obtained in step (c) to afford 5,6 dimethoxy-2-(pyridin-4-yl)- methylene indan-1-one of Formula (IV);

- e) suspending the compound of Formula (IV) and Palladium on carbon in alcoholic solvent comprising of methanol, ethanol, n-propanol, isopropanol, n-butanol or tertiary butanol, preferably methanol in presence of acetic acid in hydrogenation vessel;
- f) heating the reaction mixture of step (e) under 1-5 atmospheric hydrogen pressure at a temperature of 40 to 90° C, preferably at a temperature of 60-65°C till the reaction substantially completes;
- g) cooling of the reaction mass of step (f) to ambient temperature followed by filtering the catalyst;
- h) distilling the solvent from the filtrate obtained in step (g) to get the residue;
- i) dissolving the residue obtained in step (h) in water and followed by washing with a chloro solvent comprising of dichloromethane, dichloroethane, chloroform or carbon tetrachloride, preferably dichloromethane and separating the aqueous layer;
- j) adjusting the pH of the aqueous layer of step (i) to 9 to 14 with a base solution comprising of sodium hydroxide, sodium carbonate, sodium bicarbonate, potassium hydroxide, potassium carbonate or potassium bicarbonate, preferably aqueous potassium hydroxide solution;
- k) extracting the compound from the basified aqueous layer of step (j) with an organic solvent comprising of dichloromethane, chloroform, dichloroethane, toluene, ethyl acetate, isopropyl ether, methyl tertiary butyl ether, diethyl ether or petroleum ether, preferably dichloromethane;

- l) distilling the solvent from the reaction solution of step (k) followed by triturating the residue in non-polar organic solvents comprising of n-hexane, n-heptane, cyclohexane, cyclo heptane or petroleum ether, preferably petroleum ether or ether solvents comprising of di ethyl ether, di isopropyl ether, di isobutyl ether or methy tertiary butylether to afford 5,6-dimethoxy-2-piperidin-4-yl methyl-indan-1-one of Formula (VI);
- m) reacting the compound of Formula (VI) with benzyl bromide in alcoholic solvents comprising of methanol, ethanol isopropanol, butanol or ketone solvents comprising of acetone, éthylmethyl ketone, 2-butanone in the presence of a base inorganic base comprising of sodium carbonate, sodium bicarbonate, potassium carbonate or potassium bicarbonate or organic base comprising of triethyl amine, tributyl amine, tertiary butyl amine or pyridine at a temperature of 30-80°C, preferably at 50°C till the reaction substantially completes;
- n) cooling the reaction mass to ambient temperature and followed by filtering the mass;
- o) diluting the filtrate obtained in step (n) with water and further extracting the compound into ether solvents comprising isopropyl ether, methy tertiary butylether or diethyl ether or aromatic hydrocarbon solvents comprising of toluene, benzene, ethyl benzene, xylene, preferably toluene or aliphatic hydrocarbon solvents comprising of hexane, cyclohexane or petroleum ether.

p) distilling the solvent from the reaction solution of step (o) followed by triturating the residue in non-polar organic solvents comprising of n-hexane, n-heptane, cyclohexane, cyclo heptane or petroleum ether, preferably petroleum ether or ether solvents comprising of di ethyl ether, di isopropyl ether, di isobutyl ether or methy tertiary butylether to afford the title compound Donepezil of Formula (I).



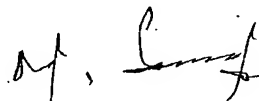
2. The process as claimed in claim (1) of step (c), where in said aqueous basic solution is 10% w/v sodium bicarbonate solution.
3. The process as claimed in claim (1) of step (e), where in the catalyst for catalytic hydrogenation is either 5% or 10% Palladium over carbon.
4. The process as claimed in claim (1) and (3), where in the catalyst for catalytic hydrogenation is 5% Palladium over carbon
5. The process as claimed in claim (1) of step (e), where in said hydrogenation is carried out in the presence of 1 to 5 mole ratio of acetic acid with respect to the compound of Formula (IV), preferably the mole ratio of acetic acid is 1.0 to 1.5.

6. The process as claimed in claim (1) of step (e), where in the reaction temperature is 40-90°C.
7. The process as claimed in claims (1) and (6), where in the reaction temperature is 60-65°C.
8. The process as claimed in claim (1) of step (e), where in the pressure of hydrogen gas is 1 to 5 atmospheres.
9. The process as claimed in claim (1) of step (i), where in the chloro solvent is dichloromethane.
10. The process as claimed in claim (1) of step (j), where in the aqueous base solution is 10% w/v potassium hydroxide solution.
11. The process as claimed in claim (1) of step (l), where in the non-polar solvent for trituration is petroleum ether.
12. The process as claimed in claim (1) of step (m), where in the said alcoholic solvent is ethanol.
13. The process as claimed in claim (1) of step (m), where in the inorganic base is sodium carbonate.
14. The process as claimed in claim (1) of step (m), wherein the reaction temperature is 55-60°C.
15. The process as claimed in claim (1) of step (o), wherein the aromatic hydrocarbon solvent is toluene.

16. The process as claimed in claim (1) of step (p), where in the non-polar solvent for trituration is petroleum ether.
17. The improved process for the preparation of Donepezil is substantially as herein described and exemplified with reference to particular examples.

Dated: 23rd day of July 2002.

Signed)

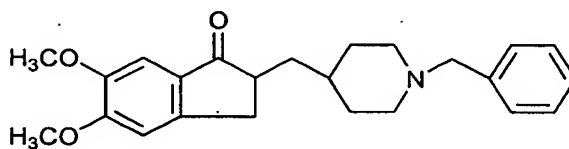


Dr. Manne Satyanarayana Reddy,
Vice-President (R&D),
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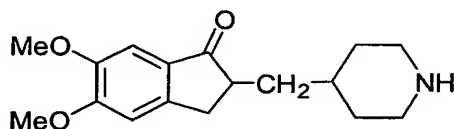
ABSTRACT

Title of the invention: An Improved Process for the Preparation of 2,3-Dihydro-5,6-dimethoxy-2[[1-(phenyl methyl)-4-piperidinyl] methyl]-1H-inden-1-one (Donepezil).

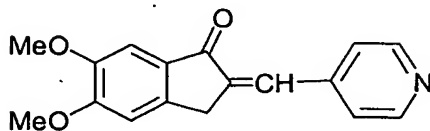
The present invention relates to an improved and convenient process for the preparation of 2,3-dihydro-5,6-dimethoxy-2[[1-(phenyl methyl)-4-piperidinyl] methyl]-1H-inden-1-one (Donepezil) and represented by Formula (I). More particularly the improved process of the present invention comprises the preparation of key intermediate of Formula (VI) by palladium-catalyzed hydrogenation of compound of Formula (IV), followed by its conversion to Donepezil with an overall yield of 84.60%.



Formula-I



Formula-VI



Formula-IV